IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

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JFW

In re Patent Application of Atty Dkt. LCM-1331-352
C# M#
von BORSTEL et al TC/A.U.: 1623
Serial No. 09/930,494 Examiner: Patrick T. Lewis
Filed: August 16, 2001 Date: May 17, 2007

Title: COMPOSITIONS AND METHODS FOR TREATMENT OF MITOCHONDRIAL DISEASES

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

☐ **Correspondence Address Indication Form Attached.**

☐	**NOTICE OF APPEAL** Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the Examiner twice/finally rejecting applicant's claim(s).	$500.00 (1401)/$250.00 (2401)	$ 0.00
☒	An Amended Appeal **BRIEF** is attached in the pending appeal of the above-identified application	$500.00 (1402)/$250.00 (2402)	$ 0.00
☐	Credit for fees paid in prior appeal without decision on merits		-$ (0.00)
☐	A reply brief is attached.		**(no fee)**
☐	Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ☐ "Small entity" statement attached.	One Month Extension $120.00 (1251)/$60.00 (2251) Two Month Extensions $450.00 (1252)/$225.00 (2252) Three Month Extensions $1020.00 (1253/$510.00 (2253) Four Month Extensions $1590.00 (1254/$795.00 (2254)	$ 0.00
	Less month extension previously paid on		-$(0.00)
		TOTAL FEE ENCLOSED	$ 0.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

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MAY 17 2007
PATENT & TRADEMARK OFFICE

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In re Patent Application of
von BORSTEL et al
Serial No. 09/930,494
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* *

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SUBMISSION OF AMENDED APPEAL BRIEF

Sir:

In response to the Notice of Non-Compliant Appeal Brief mailed April 17, 2007, Applicant submits the "Summary of Claimed Subject Matter" section in its entirety, with a concise explanation of the subject matter defined in each of the independent claims involved in the appeal. No new matter is entered.

TABLE OF CONTENTS

(I) REAL PARTY IN INTEREST

The real party in interest is Wellstat Therapeutics Corporation (previously known as Pro-Neuron, Inc.), a corporation of the State of California.

(II) RELATED APPEALS AND INTERFERENCES

The appellant, the undersigned, and the assignee are not aware of any related appeals, interferences, or judicial proceedings (past or present), which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(III) STATUS OF CLAIMS

Claims 1-15, 18-41 and 47-49 are pending and have been rejected. Claims 16, 17, 42-46 and 50 have been canceled. Claims 1-15, 18-41 and 47-49 are appealed.

No claims have been substantively allowed.

(IV) STATUS OF AMENDMENTS

No amendment has been filed since mailing of the final rejection on April 12, 2006.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

The invention of claim 1 relates to a method for treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction in a mammal comprising administering to the mammal in need of such treatment or prevention an effective amount of a pyrimidine nucleotide precursor (page 5, fourth complete paragraph, and page 18 onwards). The invention of claim 33 provides a method for preventing death or functional decline of post-mitotic cells in a mammal due to mitochondrial respiratory chain dysfunction comprising administration of an effective amount of a pyrimidine nucleotide precursor (page 5, last complete paragraph, and page 18 onwards). The invention of claim 37 provides a method for treating developmental delay in cognitive, motor, language, executive function, or social skills in a mammal comprising administration of an effective amount of a pyrimidine nucleotide (page 6, first complete paragraph, and page 18 onwards).

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are as follows:

(1) The rejection of claims 1-15, 18-32 and 47-49 under 35 U.S.C. §112, first paragraph, on lack of enablement grounds.

(2) The rejection of claims 33-36 under 35 U.S.C. §112, first paragraph, on lack of enablement grounds.

(3) The rejection of claims 1-15, 18-32 and 37-41 under 35 U.S.C. §103(a) as unpatentable over Page et al., *Proc Natl. Acad. Sci. USA*, Vol. 94, 11601-1166 (1997) in combination with U.S. 6,316,426 to von Borstel et al.

Claims 1-15, 21, 23, 31-32, 37-41 and 47 also stand rejected as constituting obviousness-type double patenting over claims 48-59 of copending Application Serial No. 09/763,955. However, Applicants have already indicated on the record that a Terminal Disclaimer will be submitted when allowable subject matter is indicated.

(VII) ARGUMENT

I. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTIONS

Claims 1-15, 18-32 and 47-49 stand rejected under 35 U.S.C. §112, first paragraph, for the reasons of record as set forth in the Official Action mailed July 26, 2005, namely that the specification, while enabling for the treatment of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction, allegedly does not reasonably provide enablement for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction. Claims 33-36 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Reversal of these rejections is respectfully requested.

The Final Action, at page 4, asserts that the references relied upon in support of Applicants' position are not sufficient to overcome the rejection because they were published in 2003, later than the date of filing of the present application in 2001. The Action asserts that: "Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing." However, in this case, the references are being relied upon to show how someone of ordinary skill would have understood the term "prevention" as used in the context of the presently claimed invention as of 2001. It is Applicants' position that the understanding of one of ordinary skill would not have changed significantly if at all

over the time period from the 1998 priority date of the present application to the date of the references in 2003. The Action (page 5) counters this position by asserting that:

> "...during patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification. This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In the instant case, the specification does not provide a definition of "prevention". In the absence of an express intent to impart a novel meaning to the claim terms, the words are presumed to take on the ordinary and customary meanings attributed to them by those of ordinary skill in the art."

In response, the correct connotation of "preventing" as used in the presently claimed invention, and as supported by the data presented in the specification, is the prophylactic administration of compounds of the invention which prevents progression or full manifestation of diseases related to essentially irreversible mitochondrial defects. Hereditary mitochondrial diseases typically involve genetic defects in genes coding proteins that, directly or indirectly, affect mitochondrial respiration. Diseases of acquired mitochondrial dysfunction, which may include Alzheimer's Disease, also have essentially permanent molecular defects disrupting mitochondrial respiration. The concept of "prevention" in the context of this class of diseases relates to clinical expression of symptoms stemming from the (permanent) genetic defect. The idea of prevention does not relate to preventing or reversing genetic defects but, rather, compensating for them to prevent full clinical manifestation of their disorder.

Prevention in the context of the present invention therefore applies to reducing the rate of progression of a chronic, worsening disease process compared with patients who do not receive the drug. In most cases, this will fall under the heading of "treatment" of a diagnosed disease but, in other situations, e.g. where a genetic disorder has not yet (but eventually will) cause clinical symptoms (e.g. in Huntington's Disease,

where a hereditary defect leads to adult onset of the disease after a nonsymptomatic earlier life) or Alzheimer's Disease, when a patient can be detected occur before actually meeting the diagnostic criteria for Alzheimer's Disease, the concept of prevention is medically and scientifically legitimate. Thus, in a patient with a genetic diagnosis of Huntington's Disease, administration of compounds of the invention may prevent onset of debilitating symptoms, lessen their severity once they do manifest, or slow the rate of progression.

In medical practice, these types of outcomes in progressive diseases are considered successful preventative interventions. In animal experiments, including several examples in the instant application (discussed below), prophylactic administration of triacetyluridine reduces the effects of subsequent administration of mitochondrial toxins, e.g. 3-nitropropionic acid and MPTP. Subsequent experiments with the Complex IV inhibitor sodium azide yielded similar results (see Example 12 of the present case, which also demonstrated reduction of cell loss in the nervous system). It is not that the administered drug (triacetyluridine) prevented the chemical lesion caused by the toxin (and it likewise does not reverse the genetic lesion in a patient with hereditary or congenital mitochondrial disease) but, rather, it attenuated the physiological consequences of the chemical lesion, including prevention of mortality in some cases.

The data included in the present application involves both "treatment" and "neuroprotective" effects of a pyrimidine nucleotide precursor(s), used as a therapeutic for disorders involving mitochondrial respiratory chain enzyme impairment. The experimental approach involved initiating treatment with the pyrimidine nucleotide

precursor triacetyluridine prior to the administration of the mitochondrial toxin. The complex I respiratory chain inhibitor MPTP model of Parkinson's disease (PD) (Example 7), Complex II respiratory chain inhibitor 3-nitropropionic acid model of Huntington's disease (HD) (Example 9) and the Complex IV respiratory chain inhibitor azide model of Alzheimer's disease (AD) (Example 12) included pretreatment with triacetyluridine. The treatment with triacetyluridine continued throughout the course of these examples. The sum therapeutic effect of triacetyluridine in the PD and HD and stroke models was a combined neuroprotective/cytoprotective and treatment effect. In the Complex IV respiratory chain inhibitor azide model of AD, there was a decrease in mortality due to pretreatment with triacetyluridine. If the mitochondrial impairment was not extremely severe (as was the case with the use of azide at only the 40 µg/hr dose), pretreatment/treatment with triacetyluridine was able to completely prevent mortality.

Based on the above, it would be understood by one of ordinary skill in reading the specification that "preventing" as used in the presently claimed invention means the prophylactic administration of compounds of the invention which prevents progression or full manifestation of diseases related to essentially irreversible mitochondrial defects. Just as few or no other classes of drugs used for treatment of chronic diseases prevent or reverse all symptoms completely, the standard for successful prevention in medical practice is prevention of symptoms of a disorder (especially a progressive or episodically exacerbating disorder) from being as bad as it would be without the drug. This is particularly significant for mitochondrial disorders which, as a class, often undergo exacerbations, either episodically or permanently.

The effect of an acylated ribonucleoside derivative(s) to "prevent" diseases involving mitochondrial dysfunction can be described as a "neuroprotective" and a "cytoprotective" effect (to include non-central nervous system cells). The term "neuroprotective" has been used to refer to the ability of a therapeutic method, if given prior to the initial initiation of factors that cause the disease ("pretreatment"), to reduce the severity or delay the onset and/or slow the progression of tissue damage and functional impairment (see Exhibits M, N. and O). The *in vivo* evidence described in the present case further supports the disease preventative effects achieved by the presently claimed method.

On page 5 of the Action, the conclusory statement that "there is a tremendous amount of unpredictability and uncertainty in the art" (referring to Bren, Hollander et al., Cattaneo et al.) does not provide a basis to conclude that the present specification fails to provide an enabling disclosure with regard to the prevention aspect of the presently claimed invention. The present inventors have established via the data contained in the present specification, that "preventing" as used in the claimed invention is enabled by the prophylactic administration of compounds of the invention which prevents progression or full manifestation of diseases related to essentially irreversible mitochondrial defects.

Reversal of the lack of enablement rejection of claims 1-15, 18-32 and 47-49 is respectfully requested.

The rejection of claims 33-36 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention should also be reversed for the

reasons discussed above, that the specification provides an enabling disclosure of the subject matter of these claims. With regard to the alleged lack of description of the subject matter of claims 33-36, the specification, in the last paragraph on page 5, together with the detailed description beginning on page 18, particularly the third complete paragraph on page 31 in the discussion of treatment, reversal and/or prevention of ALS, provides sufficient description of the claimed method for preventing death or functional decline of post-mitotic cells in a mammal due to mitochondrial respiratory chain dysfunction by administering an effective amount of a pyrimidine nucleotide precursor, so as to enable one of ordinary skill to carry out the method of claims 33-36.

In light of the above, it is believed that the prevention aspect of the present invention (as well as the treatment aspect) is supported by an enabling disclosure. Reversal of the outstanding 35 USC 112, first paragraph, rejections is accordingly respectfully requested.

II. THE OBVIOUSNESS REJECTION

Claims 1-15, 18-32 and 37-41 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Page et al., *Proc Natl. Acad. Sci. USA*, Vol. 94, 11601-1166 (1997) in combination with U.S. 6,316,426 to von Borstel et al. This rejection is respectfully traversed.

Page describes the use of uridine to treat patients with a rare disease associated with excess activity of the enzyme 5'-nucleotidase, an enzyme involved in degradation of nucleotides. The finding by Page that nucleotide precursors (uridine or ribose) are

clinically useful in treating a disorder in which the only known molecular deficit is an excess of an enzyme (5'-nucleotidase) involved in nucleotide degradation, would **not** have led one of ordinary skill to suspect that uridine or ribose would be useful in treating or preventing other disease conditions which might manifest similar symptoms. In scientific publications describing these patients (see attached Exhibits P and Q), there is no indication or suggestion of evidence for mitochondrial respiratory chain dysfunction as a molecular basis for symptoms of the described disease. As noted above, patients with this condition are rare, and there are no clear implications for other diseases. Based on this, the Page disclosure clearly does not render the presently claimed invention obvious.

The above-noted deficiencies of Page are not cured by the '426 U.S. patent to von Borstel. The '426 U.S. patent discloses that acylated ribonucleoside derivatives are effective in treating a number of disorders that involve functional impairments in tissue and organ systems involving metabolic deficiencies. However, these metabolic deficiencies in the '426 US patent are not asserted to be due to respiratory chain enzyme impairment. In view of this, one of ordinary skill would not have been motivated to combine the Page and von Borstel disclosures in the context of the presently claimed invention. Absent any such motivation, no *prima facie* case of obviousness is established in this case.

The Final Action asserts (pages 7 and 8) that "Developmental delay, seizures, ataxia, recurrent infections, severe language deficit, and an unusual behavioral phenotype characterized by hyperactivity, short attention span, and poor social

interaction are 'pathophysiological consequences of mitochondrial respiratory chain dysfunction' ". This assertion is respectfully traversed.

It is not true that all of the conditions recited in the Action are necessarily 'pathophysiological consequences of mitochondrial respiratory chain dysfunction'. As it is well recognized by person of ordinary skill that unrelated diseases can have overlapping symptoms, it is equally well recognized that the effectiveness of a particular drug in treating a symptom in one disorder does not necessarily, or even generally, imply that the drug will be useful in treating other diseases with similar symptoms. For example, epilepsy or related seizure disorders may be caused by tumors, poisons, mitochondrial defects, or simply self-amplifying circuits of neural activity without other organic defects causing the seizures. Seizure episodes in a susceptible person can be triggered by progesterone deficits, e.g. associated with the menstrual cycle. Although the clinical symptoms – seizures – may look similar, the treatments will vary according to the underlying problem.

Valproate (Depakote) is a widely-used anti-seizure medication, but it can actually exacerbate seizures (and other manifestations of mitochondrial disease) caused by mitochondrial deficits, due to its inhibitory effect on mitochondrial respiration. For someone with seizures triggered by a progesterone deficit, progesterone or an analog thereof is more appropriate than increased doses of other anti-seizure medications, which have debilitating side effects at higher doses. Some seizure disorders associated with foci of hyperexcitable neurons are best treated with electrodes inserted into the brain, which would be inappropriate for seizures caused by metabolic deficits. As evidence of this, attention is directed to Exhibits A-D, which are briefly discussed below.

Lam et al (Eur J Pediatr. 1997 Jul;156(7):562-4. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy. Lam CW, Lau CH, Williams JC, Chan YW, Wong LJ. Department of Pathology, Princess Margaret Hospital, Lai Chi Kok, Hong Kong) (Exhibit A) have reported that:

> "...valproate should not be given to patients suspected of having mitochondrial diseases. In addition, for patients whose seizures worsen with valproate therapy, an inborn error of mitochondrial metabolism should be suspected. The underlying mitochondrial DNA defects should be sought for family screening and genetic counselling."

Likewise, Krahenbuhl et al (Liver. 2000 Jul;20(4):346-8; Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure. Krahenbuhl S, Brandner S, Kleinle S, Liechti S, Straumann D. Department of Clinical Pharmacology, University of Berne, Switzerland) (Exhibit B) have reported that "Mitochondrial diseases should therefore be considered as a risk factor for valproate-induced liver failure and be excluded before treatment with valproate."

Another example of a condition which can arise from different causes is arthritis. Pain in the joints can be caused by autoimmune attack (rheumatoid arthritis, psoriatic arthritis, or lupus-associated), osteoarthritis, infections, e.g. lime disease, gout, deposition of antibody complexes, etc. All of these disorders may present with joint pain as a predominant symptom, but the appropriate treatments are very different for each of these different diseases that underlie similar symptoms, e.g. anti-TNF therapies for rheumatoid arthritis, B-Cell suppressors for Lupus, nonsteroidal anti-inflammatory drugs for osteoarthritis, antibiotics for Lyme disease, allopurinol for gout. Attention in this regard is directed to Ritchie et al., "Diagnostic Approach to Polyarticular Joint Pain",

American Family Physician, 68, 6, 1151-1160 (2003) (Exhibit C), which states (in the Abstract) that "Identifying the cause of polyarticular joint pain can be difficult because of the extensive differential diagnosis." As a consequence, "...family physicians need to keep the diagnosis open in evaluating patients who present with pain in multiple joints." (page 1151, left hand column).

Many other examples are possible in which symptoms themselves provide inadequate information for determining their cause and appropriate treatment. Developmental delays may arise from a variety of underlying causes, including metabolic defects such as phenylketonuria, lead or mercury poisoning, epilepsy, or a variety of genetic defects. A diet low in phenylalanine helps patients with phenylketonuria (in which an enzyme deficiency prevents phenylalanine metabolism), but is useless in other conditions involving developmental delay or seizures. Lead and mercury poisoning can perhaps helped by administration of chelating agents which are useless in diseases not caused by heavy metals. Antiepileptic drugs like valproate or lamictal can help developmental delays secondary to disruptions in brain function caused by seizures, but may be detrimental in disorders not caused by seizures.

The relationship between the molecular anomaly, 5'nucleotidase excess, and symptoms in the children described by Page et al. is not clear. As the authors point out, the disorder is not associated with actual uridine nucleotide deficits (and the symptoms do not match those of the only known pyrimidine deficit disorder, Orotic Aciduria). Uridine and related pyrimidine compounds were initially tested in these patients because the first one identified presented with megaloblastic anemia (a primary symptom of orotic aciduria), which was later attributed to her anti-seizure medication.

The finding that uridine was helpful was actually fortuitous and does not provide a basis for asserting that uridine would be helpful in similar symptoms or symptom complexes associated with other diseases.

In addition, the cited Page et al paper is not the first publication of the use of uridine to treat 5'-nucleotidase excess. This was published earlier in Page, et al., "A Syndrome of Megaloblastic Anemia, Immunodeficiency, and Excessive Nucleotide Degradation," in Purine and Pyrimidine Metabolism in Man VII, Part B, Harkness, et al. eds (1991) pp. 345-348 (Exhibit D). The fact that between 1991 and the subject invention no one used uridine compounds to treat pathophysiological consequences of mitochondrial respiratory chain dysfunction is further evidence of its nonobviousness.

Prior to the effective filing date of the subject application, a number of diseases were known to be mitochondrial in origin. Yet they were not treated with pyrimidine nucleotide precursors. This observation refutes the Office's position that it would have been obvious to treat any and all mitochondrial diseases using pyrimidine nucleotide precursors. As evidence of this, attention is directed to Exhibits E-L, which show that, while various types of therapies for mitochondrial disorders have been suggested (including, for example, administration of vitamins, cofactors, antioxidants, nutrients, buffers for intracellular ATP, free radical scavengers, NOS inhibitors), the method of administering a pyrimidine nucleotide precursor according to the present invention has not been suggested.

In light of the above, it is believed that a *prima facie* case of obviousness has not been generated in this case. Reversal of the obviousness rejection is respectfully requested.

III. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-15, 21, 23, 31-32, 37-41 and 47 stand provisionally rejected on obviousness-type double patenting grounds as allegedly unpatentable over claims 48-59 of copending Application Serial No. 09/763,955. Applicants will consider filing a Terminal Disclaimer when otherwise allowable subject matter is indicated.

CONCLUSION

In conclusion it is believed that the outstanding rejections should be reversed. Such action is respectfully requested.

Respectfully submitted,

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(VIII) CLAIMS APPENDIX

1. A method for treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction in a mammal comprising administering to said mammal in need of such treatment or prevention an effective amount of a pyrimidine nucleotide precursor.

2. A method as in claim 1 wherein said respiratory chain dysfunction is caused by a mutation, deletion, or rearrangement of mitochondrial DNA.

3. A method as in claim 1 wherein said respiratory chain dysfunction is caused by defective nuclear-encoded protein components of the mitochondrial respiratory chain.

4. A method as in claim 1 wherein said respiratory chain dysfunction is caused by aging.

5. A method as in claim 1 wherein said respiratory chain dysfunction is caused by administration of cytotoxic cancer chemotherapy agents to said mammal.

6. A method as in claim 1 wherein said respiratory chain dysfunction is a deficit in mitochondrial Complex I activity.

7. A method as in claim 1 wherein said respiratory chain dysfunction is a

deficit in mitochondrial Complex II activity.

8. A method as in claim 1 wherein said respiratory chain dysfunction is a deficit in mitochondrial Complex III activity.

9. A method as in claim 1 wherein said respiratory chain dysfunction is a deficit in mitochondrial Complex IV activity.

10. A method as in claim 1 wherein said respiratory chain dysfunction is a deficit in mitochondrial Complex V activity.

11. A method as in claim 1 wherein said pyrimidine nucleotide precursor is selected from the group consisting of uridine, cytidine, an acyl derivative of uridine, an acyl derivative of cytidine, orotic acid, an alcohol ester of orotic acid, or a pharmaceutically acceptable salt thereof.

12. A method as in claim 11 wherein said pyrimidine nucleotide precursor is an acyl derivative of cytidine.

13. A method as in claim 11 wherein said pyrimidine nucleotide precursor is an acyl derivative of uridine.

14. A method as in claim 11 wherein said acyl derivative of uridine is 2',3',5'-

tri-O-acetyluridine.

15. A method as in claim 11 wherein said acyl derivative of uridine is 2',3',5'-tri-*O*-pyruvyluridine.

18. A method as in claim 11 wherein said pyrimidine nucleotide precursor is administered orally.

19. A method as in claim 11 wherein said pyrimidine nucleotide precursor is administered in a dose of 10 to 1000 milligrams per kilogram of bodyweight per day.

20. A method as in claim 11 wherein said pyrimidine nucleotide precursor is administered in a dose of 100 to 300 milligrams per kilogram of bodyweight per day.

21. A method as in claim 1 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is a congenital mitochondrial disease.

22. A method as in claim 21 wherein said congenital mitochondrial disease is selected from the group consisting of Mitochondrial Encephalomyopathy, Lactic Acidemia, and stroke like episodes; Lerber's Hereditary Optic Neuropathy; Myclonic Epilepsy and "Ragged Red" (muscle) Fibers; Mitochondrial neurogastrointestinal encephalomyopathy; Neurogenic muscle weakness, Ataxia and Retinitis Pigmentosa; Progressive External Ophthalmoplegia; Leigh's Disease; and Kearns-Sayres

Syndrome.

23. A method as in claim 1 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is a neurodegenerative disease.

24. A method as in claim 23 wherein said neurodegenerative disorder is Alzheimer's Disease.

25. A method as in claim 23 wherein said neurodegenerative disorder is Parkinson's disease.

26. A method as in claim 23 wherein said neurodegenerative disorder is Huntington's Disease.

27. A method as in claim 23 wherein said neurodegenerative disorder is age-related decline in cognitive function.

28. A method as in claim 1 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is a neuromuscular degenerative disease.

29. A method as in claim 28 wherein said neuromuscular degenerative disease is selected from the group consisting of muscular dystrophy, myotonic dystrophy, chronic fatigue syndrome, and Friedreich's Ataxia.

30. A method as in claim 1 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is developmental delay in cognitive, motor, language, executive function, or social skills.

31. A method as in claim 1 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is selected from the group consisting of epilepsy, peripheral -neuropathy, optic neuropathy, autonomic neuropathy, neurogenic bowel dysfunction, sensorineural deafness, neurogenic bladder dysfunction, migraine, and ataxia.

32. A method as in claim 1 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is selected from the group consisting of renal tubular acidosis, dilating cardiomyopathy, steatohepatitis, hepatic failure, and lactic acidemia.

33. A method for preventing death or functional decline of post-mitotic cells in a mammal due to mitochondrial respiratory chain dysfunction comprising administration of an effective amount of a pyrimidine nucleotide precursor.

34. A method as in claim 33 wherein said post-mitotic cells are neurons.

35. A method as in claim 33 wherein said post-mitotic cells are skeletal

muscle cells.

36. A method as in claim 33 wherein said post-mitotic cells are cardiomyocytes.

37. A method for treating developmental delay in cognitive, motor, language, executive function, or social skills in a mammal comprising administration of an effective amount of a pyrimidine nucleotide.

38. A method as in claim 37 wherein said developmental delay is pervasive developmental delay or pervasive developmental delay – not otherwise specified.

39. A method as in claim 37 wherein said developmental delay is Attention Deficit/Hyperactivity Disorder.

40. A method as in claim 37 wherein said developmental delay is Rett's Syndrome.

41. A method as in claim 37 wherein said developmental delay is autism.

47. A method as in Claim 1 further comprising administering pyruvic acid, a pharmaceutically acceptable salt thereof, or a pyruvic acid ester.

48. A method as in claim 1 further comprising administering to the mammal an amount of creatine such that the combined amount of creatine and the pyrimidine nucleotide is effective to treat said consequences of mitochondrial respiratory chain dysfunction.

49. A method as in claim 48 wherein said pyrimidine nucleotide is 2',3',5'-tri-O-acetyluridine.

(IX) EVIDENCE APPENDIX

Exhibit A: Lam et al (Eur J Pediatr. 1997 Jul;156(7):562-4 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit B: Krahenbuhl et al (Liver. 2000 Jul;20(4):346-8 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit C: Ritchie et al., "Diagnostic Approach to Polyarticular Joint Pain", *American Family Physician*, 68, 6, 1151-1160 (2003) (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit D: Page, et al., "A Syndrome of Megaloblastic Anemia, Immunodeficiency, and Excessive Nucleotide Degradation," in Purine and Pyrimidine Metabolism in Man VII, Part B, Harkness, et al. eds (1991) pp. 345-348 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit E: DiMauro, et al, "Mitochondrial encephalomyopathies: where next?", Revista de Neurologia (1999) 28(2):164-168 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit F: Luft, "Review: The development of mitochondrial medicine", Proc. Natl. Acad. Sci. USA (September 1994) 91: 8731-8738 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit G: Beal, "Mitochondrial dysfunction in neurodegenerative diseases", Biochimica et Biophysica Acta (1998) 1366: 211-223 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit H: Blass, "Brain metabolism and brain disease: is metabolic deficiency the proximate cause of Alzheimer dementia", J. Neurosc. Res. (2001) 66: 851-856 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit I: Bowling, et al., "Minireview: Bioenergetic and Oxidative stress in neurodegenerative diseases", Life Sciences (1995) 56(14): 1151-1171 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit J: Beal, "Mitochondria, free radicals, and neurodegeneration", Current Opinion Neurobiol. (1996) 6: 661-666 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit K: Browne, et al, "Oxidative damage and mitochondrial dysfunction in neurodegenerative diseases", Biochem. Soc. Trans. (1994) 22: 1002-1006 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit L: Schulz, et al., "Mitochondrial dysfunction in movement disorders", Current Opinion in Neurology (1994) 7:333-339 (submitted with the Response dated January 26, 2006 and entered per the Action mailed April 12, 2006).

Exhibit M: Ferrante, et al., "Neuroprotective Effects of Creatine in a Transgenic Mouse Model of Huntington's Disease"; *The Journal of Neuroscience*; 20(12), pp 4389-4397, June 15, 2000 (submitted with the Response dated April 21, 2004 and entered per the Action mailed November 3, 2004).

Exhibit N: Du et al., "Minocycline Prevents Nigrostriatal Dopaminergic Neurodegeneration in the MPTP Model of Parkinson's Disease"; *PNAS*, Vol. 98, No. 25; pp. 14469-14674 (December 4, 2001) (submitted with the Response dated April 21, 2004 and entered per the Action mailed November 3, 2004).

Exhibit O: Ravina et al., "Neuroprotective Agents for Clinical Trials in Parkinson's Disease"; *American Academy of Neurology*; 60, pp. 1234-1240 (2003) (submitted with the Response dated April 21, 2004 and entered per the Action mailed November 3, 2004).

Exhibit P: Page et al., Adv. Exp. Med. Biol. 1998; 431:789-92 (submitted with the Response dated April 21, 2004 and entered per the Action mailed November 3, 2004).

Exhibit Q: Page et al., Adv. Exp. Med. Biol. 1991; 309B:345-8 (submitted with the Response dated April 21, 2004 and entered per the Action mailed November 3, 2004).

(X) RELATED PROCEEDINGS APPENDIX

None.